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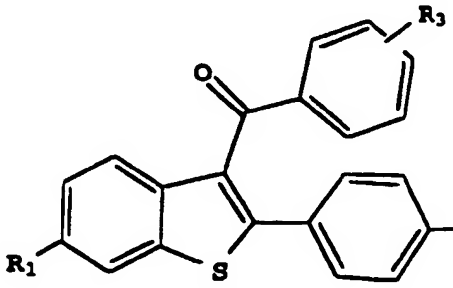
(71) Applicant: **ELI LILLY AND COMPANY**
Indianapolis, Indiana 46285 (US)

(72) Inventors:
- **Berg, David Thompson**
  Beech Grove, Indiana 46107 (US)
- **Cullinan, George Joseph**
  Trafalgar, Indiana 46181 (US)
- **Grinnell, Brian William**
  Indianapolis, Indiana 46220 (US)
- **Richardson, Mark Alan**
  Bloomington, Indiana 47408 (US)

(74) Representative: **Hudson, Christopher Mark et al**
Lilly Industries Limited
European Patent Operations
Erl Wood Manor
Windlesham Surrey GU20 6PH (GB)

(54) Benzothiophene compounds, and uses and formulations thereof

(57) Benzothiophenes, and uses and formulations thereof, are provided by the present invention. The compounds are of the formula



Ia

wherein R_1 and R_2 are independently -OH, -OCO(C_1-C_6 alkyl), -O(CO)O(C_1-C_6 alkyl), -OCO-Ar, where Ar is phenyl or substituted phenyl, or -O(CO)Ophenyl; and
R_3 is a substituent in the 3 or 4 position of the phenyl ring selected from the group of -H, -Cl, -Br, $-CH_3$, or $-CH_2CH_3$;

or a pharmaceutically acceptable salt or solvate thereof, with the proviso that when R_1 and R_2 are both hydroxy, R_3 is not -H, $-CH_3$, or $-CH_2CH_3$.

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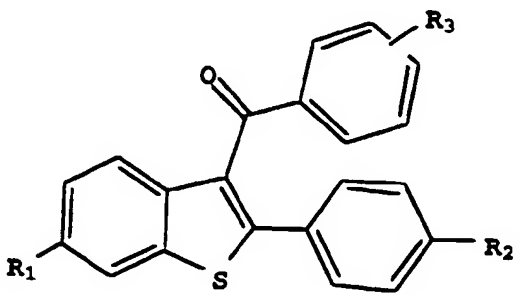
The invention also provides pharmaceutical formulations which include compounds of formula Ia.

The invention also provides methods of inhibiting PAI-1 or a physiological condition associated with an excess thereof, which includes administering to a human in need thereof an effective amount of a compound of formula Ib



Ib

wherein

R_1 and R_2 are independently -OH, -OCO(C_1-C_6 alkyl),-O(CO)O(C_1-C_6 alkyl), -OCO-Ar, where Ar is phenyl or substituted phenyl, or -O(CO)Ophenyl; and

R_3 is a substituent in the 3 or 4 position of the phenyl ring selected from the group of -H, -Cl, -Br, $-CH_3$, or $-CH_2CH_3$;

or a pharmaceutically acceptable salt or solvate thereof.

The current invention concerns the discovery of (encompassing both Ia and Ib) 2-phenyl-3-aroyl-benzo[b]thiophenes, those of formula I, and their use for inhibiting PAI-1. The methods of use provided by this invention are practiced by administering to a human in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit PAI-1 or a physiological condition associated with an excess thereof. The term "inhibit" includes its generally accepted meaning which includes prohibiting, preventing, restraining, and slowing, stopping, or reversing progression, severity, or ameliorating a resultant symptom or effect.

General terms used in the description of compounds herein described bear their usual meanings. For example, "C_1-C_6 alkyl" refers to straight or branched aliphatic chains of 1 to 6 carbon atoms including methyl, ethyl, propyl, isopropyl, n-butyl, pentyl, iso-pentyl, hexyl, and the like.

The term "substituted phenyl" refers to a phenyl group having one or more substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_3 alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl. "C_1-C_3 alkoxy" refers a C_1-C_3 alkyl group attached through an oxygen bridge such as , methoxy, ethoxy, n-propoxy, iso-propoxy.

Compounds of the invention include the following:

[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [4-chlorophenyl]methanone
[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [3-chlorophenyl]methanone
[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [4-fluorophenyl]methanone
[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [3-fluorophenyl]methanone
[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [4-ethylphenyl]methanone
[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [3-ethylphenyl]methanone
[2-(4-acetyloxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [4-methylphenyl]methanone
[2-(4-hydroxyphenyl)-6-acetyloxybenzo[b]thien-3-yl] [4-methylphenyl]methanone
[2-(4-acetyloxyphenyl)-6-acetyloxybenzo[b]thien-3-yl] [4-methylphenyl]methanone
[2-(4-hydroxyphenyl)-6-benzoyloxybenzo[b]thien-3-yl] [4-chlorophenyl]methanone

A preferred embodiment of this invention is [2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [phenyl]methanone.

The compounds of formula I are derivatives of the benzo[b]thiophene structure which is named and numbered according to the Ring Index, The American Chemical Society, as follows:

to protecting and deprotecting hydroxyl functions (see: e.g., J.W. Barton, "Protective Groups in Organic Chemistry:, J. G W. McOmie (ed.) Plenum Press. New York. NY, 1973 Chapter 2, and T. W. Green, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. Chapter 7).

Preparation 1

2-(4-Methoxyphenyl)-6-methoxybenzo[b]thiophene.

To 700 mL of EtOH were added 50 g (0.356 mmol) of 3-methoxythiophenol. To the mixture then were added 20g (o.36 mmol) of KOH pellets followed by 82.5 g (0.36 mmol) of a-bromo-4-methoxyacetophenone added in small portions. The entire addition was carried out at about 25° C. Upon completion of the addition, the reaction mixture was stirred for three hours at room temperature. The EtOH was evaporated, and a residual oil was taken up in 2 L of water and 1.5 L of ether. The ether was separated, washed with water, dried over $MgSO_4$, and evaporated to dryness. The resulting crystalline residue was homogenized in a blender using a 3:1 mixture of ether and petroleum ether. The solid was filtered and dried to give 78.5 g (76%) of a-(3-methoxyphenylthio)-4-methoxyacetophenone as pink crystals.
MP: 53-54°C
EA: Calc. for $C_{16}H_{16}O_3S$: C, 66.64: H, 5.59; O, 16.64; S, 11.12 Found: C, 66.55; H, 5.87: O, 16.82; S, 10.86.

The above product was cyclized and isomerized by adding 50g (0.173 mmol) of the product to 250 g of polyphosphoric acid preheated to 95° C. The mixture was vigorously stirred, and the temperature rose to 115-120° C. Monitoring by tlc indicated that the reaction was virtually over after five minutes. At the end of thirty minutes, ice was added to the mixture. The temperature then rose to 130° C. at which time additional ice was added. Crystals appeared: water was added to the mixture, and the product was collected by filtration. The resulting tan solid was slurried in hot MeOH, cooled, and filtered. The solid was recrystallized from 2.5 L of EtOAc to obtain 30 g of the title compound.
MP: 193-194°C
EA: Calc. for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; O, 11.84; S, 11.86 Found: C, 71.03; H, 5.30; O, 11.81; S, 11.60.

Preparation 2

[2-(4-Methoxyphenyl)-6-methoxybenzo[b]thien-3-yl] [phenyl] methanone.

3 g (11.1 mmol) of 2-(4-methoxyphenyl)-6-methoxybenzo[b]thiophene and 1.55 g (11.1 mmol) of benzoyl chloride were suspended in 150 mL of CH_2Cl_2 and cooled to 0° C. The reaction mixture was vigorously stirred and 1.6 g (12 mmol) of $AlCl_3$ was added in several portions over a ten minute time period. The reaction was allowed to proceed for one hour, after which 1 L of water was added to quench the reaction. The organic layer was separated and washed with 100 mL of 1 N NaOH, 100 mL of brine, dried by filtration through anhydrous K_2CO_3, and evaporated to dryness. The crude product was crystallized twice from MeOH. This yielded 1.85 g of the title compound as white crystalline solid.
MP: 100-102° C
PMR: Consistent with the proposed structure.

Example 1

[2-(4-Hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl][phenyl] methanone.

2.5 g (6.7 mmol) of [2-(4-methoxyphenyl)-6-methoxybenzo[b]thien-3-yl] [phenyl] methanone mixed with 10 g of pyridine hydrochloride and fused at 220° C for 1.5 hours. The reaction mixture was poured into ice-water and mixture extracted with 500 mL of EtOAc. The EtOAc layer was separated, washed with brine, dried with MgSO4, and evaporated to a yellow oil. The product was crystallized from MeOH-HOH. This yielded 2.1 g of the title compound as yellow crystalline solid.

MP: 203-205°C
PMR: Consistent with the proposed structure.
MS: m/e=346 (M)
EA: Calc. for $C_{21}H_{14}O_3S$: C, 72.81; H, 4.07; O, 13.86; S, 9.26 Found: C, 72.54; H, 4.09; O, 13.80; S, 9.23.

pound from which they are derived. and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example. the compounds can be formulated with common excipients. diluents. or carriers. and formed into tablets. capsules. suspensions. powders. and the like. Examples of excipients. diluents. and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives: binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin and polyvinyl pyrrolidone: moisturizing agents such as glycerol: disintegrating agents such as calcium carbonate and sodium bicarbonate: agents for retarding dissolution such as paraffin: resorption accelerators such as quaternary ammonium compounds: surface active agents such as cetyl alcohol, glycerol monostearate: adsorptive carriers such as kaolin and bentonite: and lubricants such as talc. calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to inhibit PAI-1, or any other use disclosed herein. and according to this invention will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need thereof from once to about three times each day, or more often as needed to effectively inhibit PAI-1, or any other use disclosed herein.

Formulations

In the formulations which follow, "Active ingredient" means a compound of formula I.

Formulation 1:	
Gelatin Capsules	
Hard gelatin capsules are prepared using the following:	
Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No 45 mesh U.S. sieve, and filled into hard gelatin capsules.

The specific formulations above may be changed in compliance with the reasonable variations provided.

A tablet formulation is prepared using the ingredients below:

Formulation 2:	
Tablets	
Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

cardioprotective effect, i.e. reduction in the incidence of cardiovascular events, due to enhancing fibrinolytic potential. Further the positive effect of compound 1 on reducing PAI-1 may provide for acute and chronic uses in conditions where elevated levels are associated with pathology or may be used to prevent such pathological conditions.

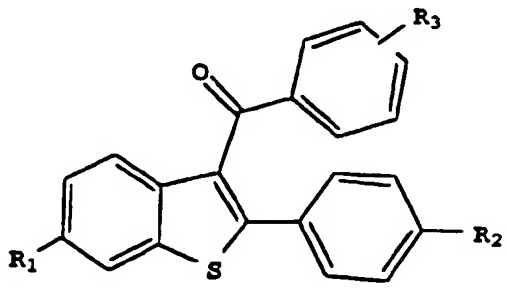
Table 1.

Effect of compound 1 on PAI-1 secretion from human endothelial cells	
Treatment	PAI-1 Induction % of IL-1 Control +/-SE*
IL-1 Control	100
IL-1 & 1 nM Compound 1	44 +/-8
IL-1 & 10 nM compound 1	36 +/-5

* (drug treated - control)/(Il-1 treated-control) X 100%

Claims

1. A compound of formula Ia:



Ia

wherein

R_1 and R_2 are independently -OH, -OCO(C_1-C_6 alkyl), -O(CO)O(C_1-C_6 alkyl), -OCO-Ar, where Ar is phenyl or substituted phenyl, or -O(CO)Ophenyl; and
R_3 is a substituent in the 3 or 4 position of the phenyl ring selected from the group of -H, -Cl, -Br, $-CH_3$, or $-CH_2CH_3$;

or a pharmaceutically acceptable salt or solvate thereof, with the proviso that when R_1 and R_2 are both hydroxy, R_3 is not -H, $-CH_3$, or $-CH_2CH_3$.

2. A compound of formula Ia of Claim 1 selected from

[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [4-chlorophenyl]methanone
[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [3-chlorophenyl]methanone
[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [4-fluorophenyl]methanone
[2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [3-fluorophenyl]methanone
[2-(4-acetyloxyphenyl)-6-hydroxybenzo[b]thien-3-yl] [4-methylphenyl]methanone
[2-(4-hydroxyphenyl)-6-acetyloxybenzo[b]thien-3-yl] [4-methylphenyl]methanone
[2-(4-acetyloxyphenyl)-6-acetyloxybenzo[b]thien-3-yl] [4-methylphenyl]methanone or
[2-(4-hydroxyphenyl)-6-benzoyloxybenzo[b]thien-3-yl] [4-chlorophenyl]methanone

3. A pharmaceutical formulation comprising a compound of formula Ia of Claim 1 and one or more excipients, diluents or carriers.

4. The use of a compound of formula Ib

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EUROPEAN SEARCH REPORT

Application Number
EP 97 30 5165

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	US 5 532 382 A (CARLSON DONALD G ET AL) * examples 9,10 *	1-5	C07D333/56 A61K31/38
A D	FR 2 329 271 A (ELI LILLY AND CO.) * examples 7,32 * & US 4 133 814 A	1-5	
A	WO 95 10513 A (PFIZER ;CAMERON KIMBERLY O (US); SILVA JARDINE PAUL DA (US); LARSO) * example 21 *	1-5	
A	CHEMICAL ABSTRACTS, vol. 115, no. 5, 5 August 1991 Columbus, Ohio, US; abstract no. 42197t, XP002044078 * abstract * & T. UCHIUMI ET AL.: INT. J. CANCER, vol. 47, no. 1, 1991, pages 80-85,	1-5	
A	CHEMICAL ABSTRACTS, vol. 111, no. 9, 28 August 1989 Columbus, Ohio, US; abstract no. 71195p, XP002044079 * abstract * & H.W. DICKERMAN ET AL.: ENDOCRINOLOGY, vol. 125, no. 1, 1989, pages 492-500,	1-5	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	21 October 1997	Frelon, D

CATEGORY OF CITED DOCUMENTS

X particularly relevant if taken alone
Y particularly relevant if combined with another document of the same category
A technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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